Dissertation On

SERUM URIC ACID IN ACUTE ISCHEMIC STROKE

submitted in partial fulfilment of
requirements for

M.D. DEGREE BRANCH I GENERAL MEDICINE

of

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY,

CHENNAI

MADRAS MEDICAL COLLEGE &

GOVT. GENERAL HOSPITAL

CHENNAI – 600 003.

MARCH 2008

CERTIFICATE

This is to certify that this dissertation entitled **"SERUM URIC ACID IN ACUTE ISCHEMIC STROKE"** submitted by **Dr. T. AARTHI PRIYA** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2008 is a bona fide record of work done by him under my direct audience and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

Director,
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Government General Hospital,
Chennai – 600 003.

DECLARATION

I solemnly declare that the dissertation titled **"SERUM URIC ACID IN ACUTE ISCHEMIC STROKE"** is done by me at Madras Medical College & Govt. General Hospital, Chennai during 2005-2008 under the guidance and supervision of **Prof. P. THIRUMALAIKOLUNDU SUBRAMANIAN, M.D.**

The dissertation is submitted to The Tamilnadu **Dr.M.G.R.Medical University** towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

Place:

Date:

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ACKNOWLEDGEMENT

I would like to thank our Dean, **Dr. T. P. Kalaniti, M.D.,** who gave me permission to do this study in our institution.

I would like to express my sincere gratitude to our Professor and Director, Institute of Internal Medicine, **Prof. Thirumalaikolundu Subramanian, M.D.,** for his guidance and encouragement. With extreme gratitude, I express my indebtedness to him for his motivation, advice and valuable criticism, which enabled me to complete this work.

I am extremely thankful to Assistant Professors of Medicine **Dr.R.Penchalaiah, M.D., Dr.K.V.S.Latha, M.D., Dr.Saravanababu, M.D.,** and **Dr. Vijayaraghavan, M.D.,** for their guidance and co-operation.

I thank all Professors, Assistant Professors, and Post-graduates of Institute of Biochemistry for their valuable support in biochemical analysis.

I would always remember with extreme sense of thankfulness for the co-operation and criticism shown by my Postgraduate colleagues.

I am immensely grateful to the generosity shown by the patients who participated in this study. If at all, this study could contribute a little to relieve them from their suffering I feel that I have repaid a part of my debt.

CONTENTS

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PROFORMA

Name	:	Ward No.	:
Sex	:	Date of Admission	:
IP No.	:		
Serial No.	:		
Age	:		
Diabetes	:		
Hypertension	:		
Previous stroke / TIA	:		
Time after stroke onset	:		
Smoking	:		
Fasting Blood Sugar	:		
Blood pressure	:		
CT Brain	:		
Serum uric acid	:		

Outcome after 2 weeks of stroke:

CONTROL CHART

S. No.	Name	Age	Sex	BP mmHg	FBS mg/dL	Serum Uric Acid Level mg/dL	Smoking
1	M	36	F	120/80	106	3.7	-
2	K	38	F	130/80	90	4.2	-
3	P	35	F	120/80	96	4.8	-
4	R	36	F	140/90	110	3.6	-
5	S	38	F	120/80	110	3.2	-
6	M	42	F	146/90	108	3.6	-
7	R	48	F	150/100	130	3.4	-
8	P	45	F	120/80	108	4.9	-
9	L	46	F	130/80	96	4.8	-
10	R	45	F	120/80	90	4.9	-
11	M	52	F	130/80	94	3.1	-
12	S	55	F	130/90	110	3.3	-
13	R	56	F	146/90	129	3.6	-
14	S	54	F	130/80	132	3.4	-
15	P	58	F	130/90	110	3.5	-
16	P	62	F	150/100	134	3.5	-
17	R	65	F	130/90	116	3.3	-
18	M	66	F	140/100	136	3.6	-
19	N	68	F	130/80	110	3.3	-
20	P	69	F	130/80	116	3.2	-
1	P	34	M	120/80	90	4.8	-
2	A	60	M	150/100	130	4.7	-
3	M	55	M	140/90	110	4.4	+
4	R	36	M	130/80	96	3.5	-
5	B	32	M	120/80	106	3.4	-
6	L	38	M	120/80	110	4.0	-
7	M	40	M	146/90	120	3.9	+
8	M	52	M	130/80	140	4.6	-
9	K	58	M	120/80	110	4.8	-
10	L	56	M	140/96	136	4.8	-
11	P	55	M	130/80	110	4.2	+
12	M	48	M	120/80	116	3.7	-
13	P	42	M	130/80	106	4.2	-
14	R	46	M	150/90	136	4.9	-
15	L	42	M	120/80	90	4.2	-
16	K	45	M	130/80	134	4.4	+
17	M	64	M	130/90	110	4.2	-
18	K	65	M	140/90	136	4.7	+
19	P	65	M	120/80	110	5.3	-
20	S	67	M	130/80	108	5.5	+

MASTER CHART

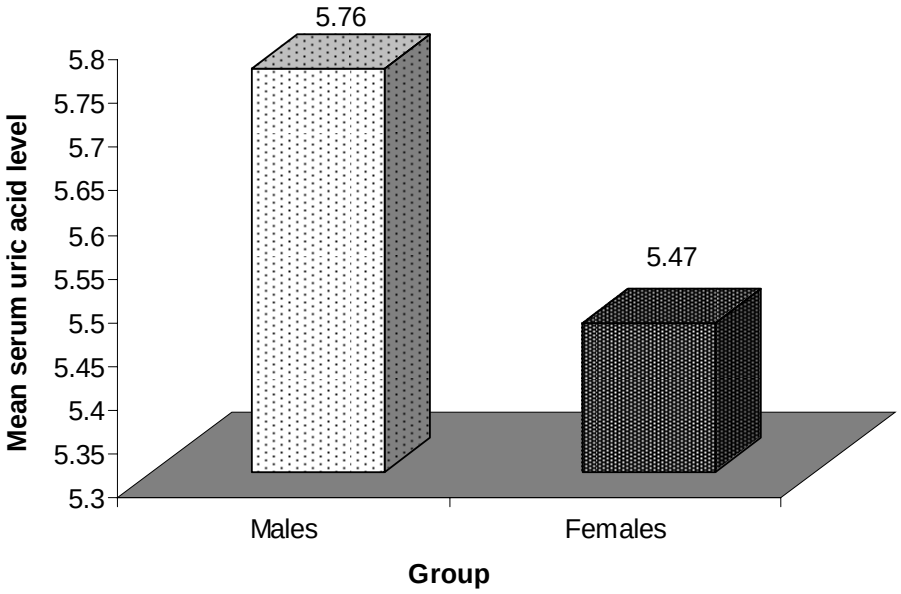
S. No.	Name	Age	Sex	BP mm/Hg	Time after onset of stroke	FBS mg/dL	Outcome scale	Serum Uric Acid Level mg/dL	Smoking
1	V	35	M	140/100	40	120	1	4.2	+
2	E	52	F	130/80	24	96	4	3.8	-
3	D	54	M	150/100	4	138	4	3.2	+
4	A	63	M	160/100	10	142	4	4.7	-
5	V	70	M	130/90	12	160	2	3.9	+
6	K	38	M	146/94	24	110	1	4.9	+
7	M	55	F	136/84	20	90	4	4.0	-
8	P	59	M	156/90	6	140	4	3.8	+
9	A	62	M	150/96	12	136	4	5.0	-
10	R	68	M	136/90	18	146	2	4.2	+
11	S	60	M	154/90	20	112	3	4.1	+
12	M	30	M	120/80	24	88	4	3.2	-
13	S	34	M	150/100	38	130	5	3.5	-
14	C	62	M	140/100	28	132	4	4.2	-
15	J	70	M	130/90	30	126	3	3.2	+
16	K	60	M	150/90	24	110	3	4.7	+
17	M	30	M	130/80	12	80	4	3.8	-
18	P	38	M	156/90	30	134	5	4.0	-
19	A	64	M	146/100	12	138	4	4.8	-
20	R	70	M	130/80	24	126	3	3.8	+
21	N	55	M	130/90	20	122	4	4.5	+
22	K	42	M	140/90	1	139	3	5.5	+
23	S	70	M	140/100	22	123	4	4.3	+
24	A	44	M	130/90	16	118	5	3.6	+
25	P	40	M	120/84	4	129	4	4.2	+
26	K	57	M	134/90	24	120	4	5.0	+
27	M	46	M	150/90	3	140	3	5.8	+
28	P	70	M	150/100	22	122	4	4.6	+
29	R	48	M	130/90	18	106	5	4.2	+
30	S	40	M	126/84	6	131	4	5.0	+

S. No.	Name	Age	Sex	BP mm/Hg	Time after onset of stroke	FBS mg/dL	Outcome scale	Serum Uric Acid Level mg/dL	Smoking
31	S	70	M	160/100	18	111	4	3.8	+
32	M	69	M	150/90	3	132	3	5.7	+
33	P	47	M	160/90	20	108	5	4.2	+
34	A	70	M	150/100	28	98	4	4.6	-
35	A	60	F	130/90	32	106	4	4.6	-
36	K	70	M	150/90	20	106	4	4.0	+
37	P	68	M	156/90	13	138	3	6.0	+
38	M	44	M	160/94	12	110	5	4.7	+
39	R	70	M	160/100	20	96	4	5.0	-
40	L	60	F	130/80	28	110	4	5.0	-
41	B	51	F	120/80	38	110	4	4.8	-
42	B	55	F	130/90	29	124	3	5.1	-
43	M	65	F	150/90	2	108	4	4.1	-
44	D	50	F	160/90	18	120	4	3.8	-
45	L	58	F	130/80	29	126	4	3.2	-
46	K	54	F	120/80	30	106	4	5.0	-
47	M	58	F	126/86	24	120	3	5.4	-
48	P	62	F	160/94	10	112	4	4.0	-
49	N	50	F	150/100	12	107	4	3.2	-
50	R	54	F	130/90	26	116	4	3.6	-
51	M	52	F	120/80	29	120	4	3.2	-
52	L	61	F	140/100	37	128	4	5.4	-
53	P	56	F	130/80	24	110	4	3.6	-
54	R	64	F	150/100	20	130	4	5.0	-
55	R	58	F	140/90	40	112	4	6.1	-
56	G	57	M	160/90	7	120	2	7.2	+
57	R	60	M	146/100	19	110	3	7.3	+
58	K	54	F	150/90	20	108	4	6.4	-
59	P	58	M	160/100	10	115	2	7.6	+
60	K	60	M	150/90	14	106	3	7.8	+
61	S	50	M	130/90	11	106	4	7.2	+
62	S	60	M	120/80	23	124	4	7.0	+
63	B	32	M	120/80	29	108	4	7.0	+

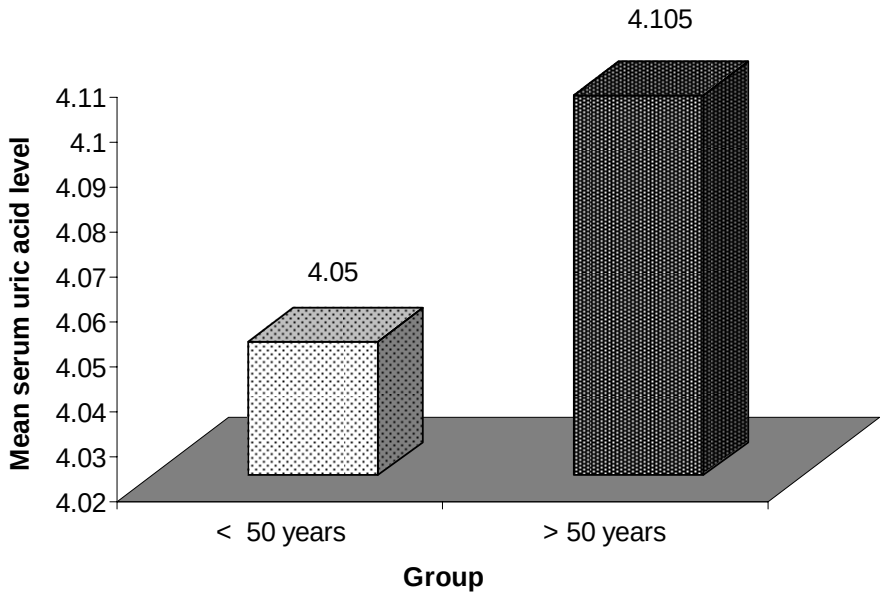
S. No.	Name	Age	Sex	BP mm/Hg	Time after onset of stroke	FBS mg/dL	Outcome scale	Serum Uric Acid Level mg/dL	Smoking
64	A	57	M	130/94	40	162	3	7.7	-
65	B	60	M	140/90	15	158	3	7.4	-
66	K	50	M	134/80	20	110	4	7.3	+
67	M	60	M	126/80	24	120	4	7.0	+
68	S	36	M	120/80	26	110	4	7.1	+
69	N	54	M	130/80	40	140	3	7.4	-
70	P	60	M	146/90	20	146	3	7.8	-
71	P	58	M	140/90	18	96	3	7.4	+
72	K	50	M	130/90	2	90	4	7.8	-
73	K	70	M	140/100	18	118	3	7.1	+
74	A	54	M	130/90	8	98	2	7.6	+
75	N	60	M	146/90	13	102	4	7.9	+
76	B	54	M	150/100	10	90	3	7.8	+
77	A	50	M	130/90	12	94	4	7.0	-
78	P	70	M	146/100	20	110	3	7.8	+
79	R	58	M	130/90	20	90	2	7.5	+
80	L	60	M	150/100	12	110	4	7.1	+
81	N	70	M	150/90	2	129	3	7.6	-
82	K	65	F	140/100	15	151	2	8.0	-
83	S	52	F	134/90	6	140	3	7.8	-
84	S	65	F	140/90	11	126	4	6.4	-
85	SK	53	F	120/80	29	122	3	6.7	-
86	P	70	M	160/100	6	130	3	7.8	-
87	B	67	F	150/90	12	146	2	7.1	-
88	L	56	F	130/80	20	136	3	6.4	-
89	R	68	F	150/100	10	128	4	5.9	-
90	M	56	F	120/80	30	110	3	6.9	-
91	P	58	F	130/80	33	116	2	6.0	-
92	G	54	F	120/80	16	120	3	7.2	-
93	A	62	F	130/80	37	122	2	6.9	-
94	A	68	F	150/100	21	101	4	7.0	-
95	S	50	M	130/90	36	100	4	7.4	-
96	S	52	M	150/100	16	96	4	7.2	-

S. No.	Name	Age	Sex	BP mm/Hg	Time after onset of stroke	FBS mg/dL	Outcome scale	Serum Uric Acid Level mg/dL	Smoking
97	R	56	F	136/90	34	116	2	6.0	-
98	L	52	F	126/80	24	110	3	6.2	-
99	M	66	F	130/80	30	120	2	6.8	-
100	K	64	F	150/100	20	110	4	6.4	-
101	R	50	M	130/80	40	106	4	7.1	-
102	R	56	M	156/100	18	90	4	7.4	-

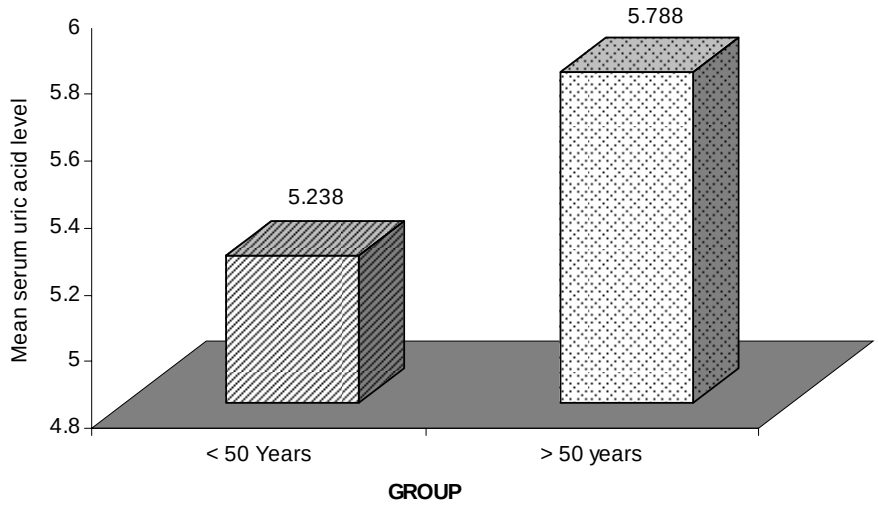
SERUM URIC ACID LEVEL BETWEEN MALES & FEMALES IN THE CASES



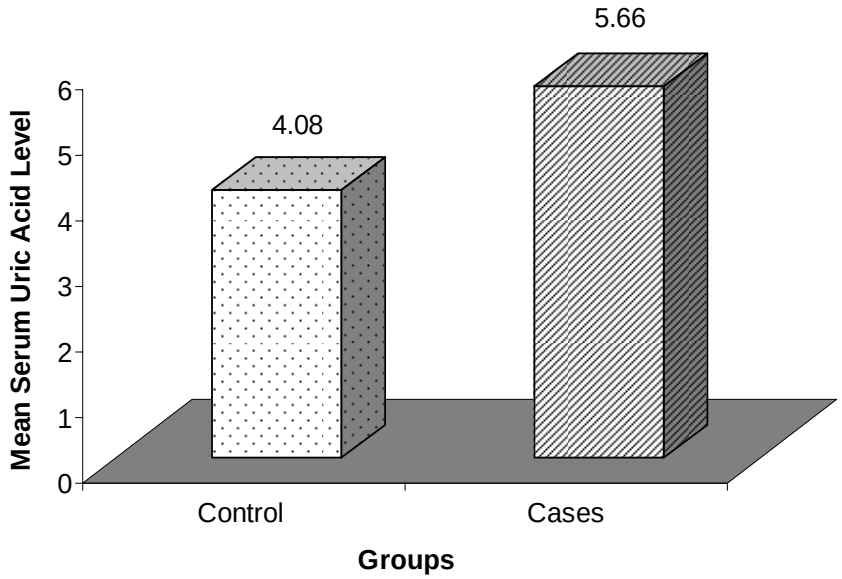
SERUM URIC ACID BETWEEN THE AGE GROUPS ≤ 50 YEARS AND > 50 YEARS AMONG CONTROL



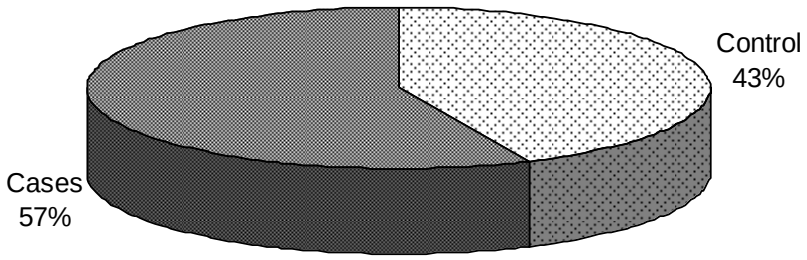
SERUM URIC ACID BETWEEN AGE GROUPS ≤ 50 YEARS & > 50 YEARS AMONG STROKE CASES



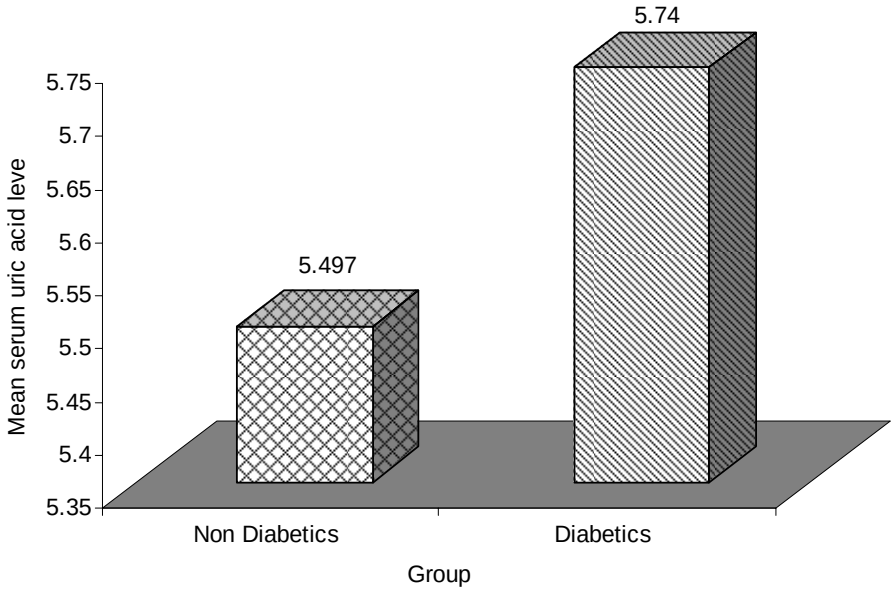
SERUM URIC ACID LEVEL BETWEEN STROKE CASES AND CONTROLS



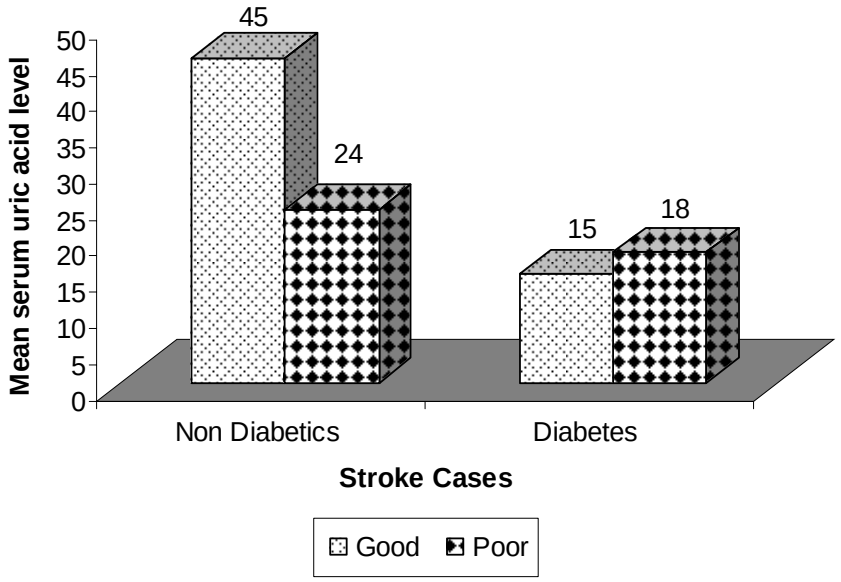
SERUM URIC ACID AMONG DIABETIC STROKE CASES AND CONTROL



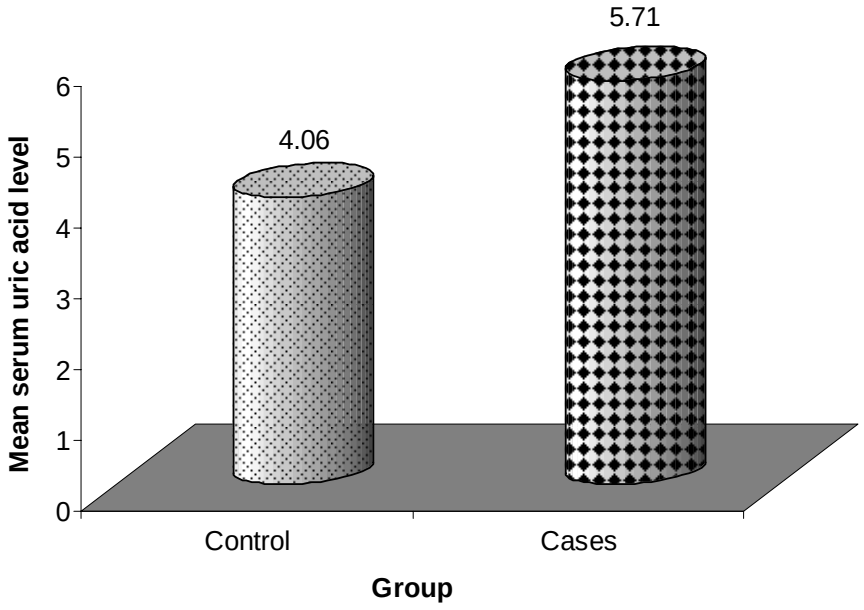
SERUM URIC ACID AMONG DIABETIC AND NON DIABETIC STROKE CASES



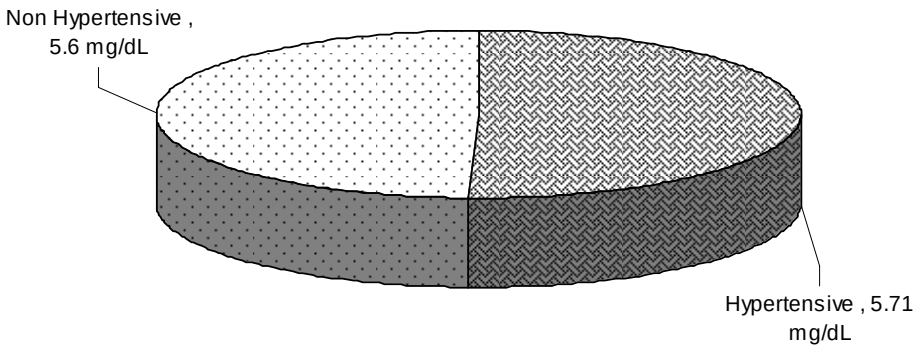
OUTCOME IN DIABETIC AND NONDIABETIC STROKE CASES



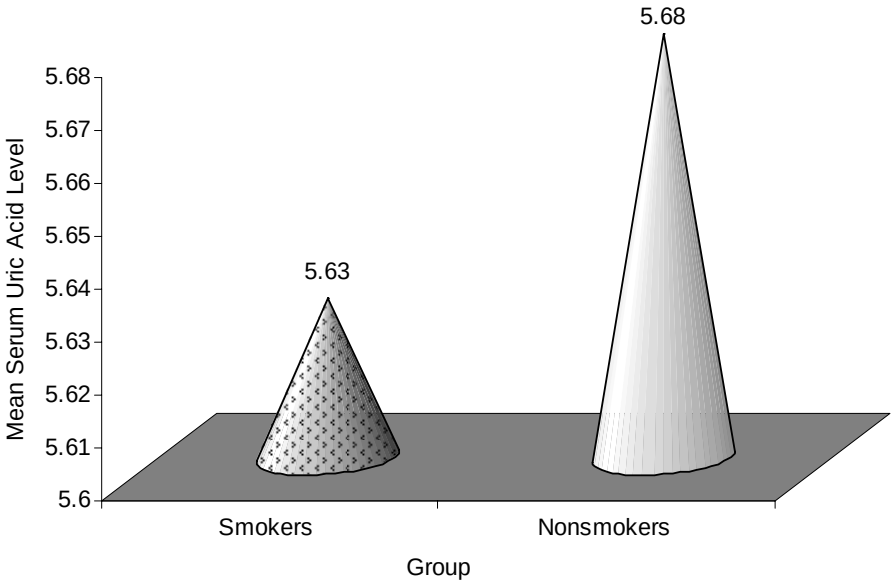
SERUM URIC ACID AMONG HYPERTENSIVE STROKE CASES & CONTROL



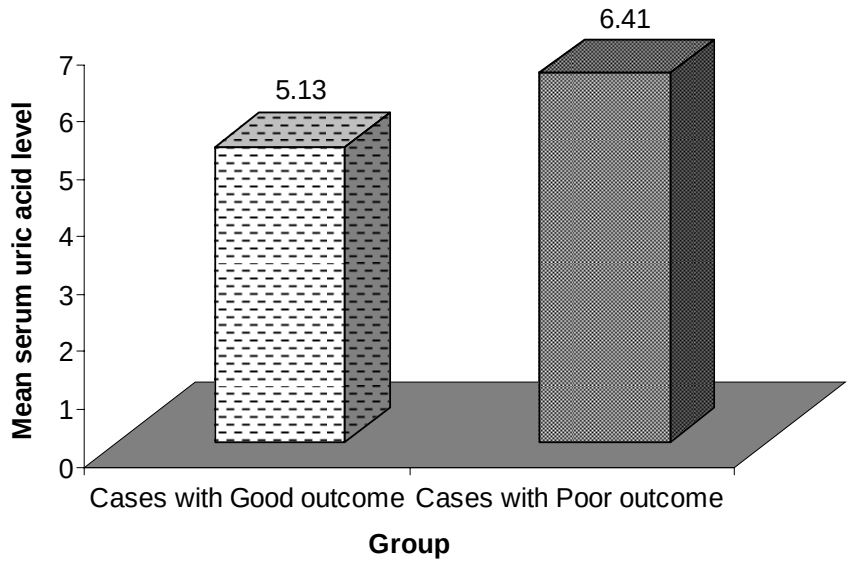
SERUM URIC ACID AMONG HYPERTENSIVES AND NON HYPERTENSIVES WITHIN STROKE CASES



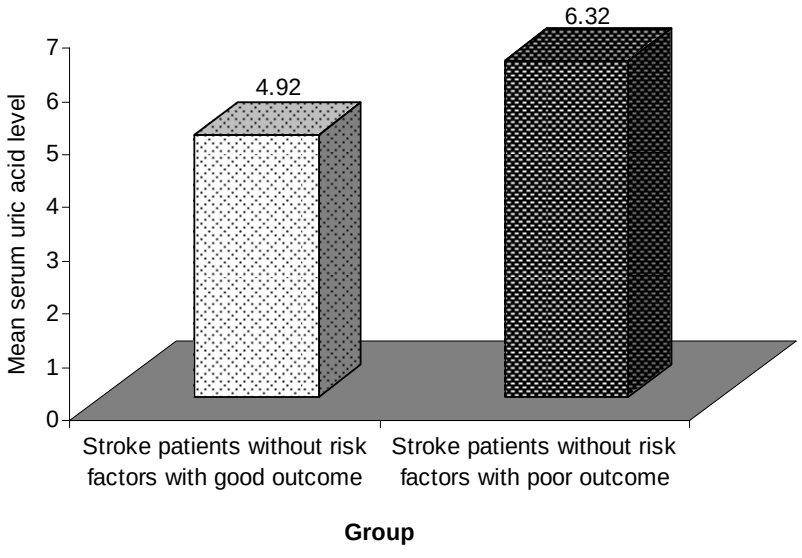
SERUM URIC ACID AMONG SMOKERS AND NON SMOKERS IN THE STROKE CASES



SERUM URIC ACID AMONG STROKE CASES IN RELATION TO OUTCOME



SERUM URIC ACID IN STROKE PATIENTS WITHOUT RISK FACTORS WITH OUTCOME



INTRODUCTION

In clinical practice, uric acid has been used as a marker of severe metabolic disturbances. Its antioxidant property has not been considered much for a longtime.

The plasma concentration of uric acid is almost 10-fold higher than other antioxidants such as Vitamin C and Vitamin E. It is considered that uric acid has much higher antioxidant capacity[1]. Uric acid which is formed by catabolism of purine is proposed to neutralize the free radical injury that occurs in ischemic stroke.

Epidemiological studies have suggested a direct relationship between the levels of the natural antioxidant uric acid and the risk of cerebrovascular and coronary ischemic events[2]. However it is not completely clear whether this association indicates that uric acid is an independent ischemic risk factor or it represents a marker of atherosclerotic disease. Whether the concentration of uric acid at the onset of ischemic symptoms influences the severity of stroke also remains to be elucidated.

AIM OF THE STUDY

1. To estimate the level of serum uric acid in patients with acute ischemic stroke

2. To findout whether there is variation related to gender and age.

3. To identify whether uric acid level among the stroke cases has any association with diabetes and hypertension.

4. To study its significance in the outcome of these patients.

REVIEW OF LITERATURE

Stroke or cerebrovascular accident by definition of WHO is a rapidly developing clinical symptoms and/or signs of focal neurological deficit and at times global loss of cerebral function (coma) lasting longer than 24 hrs or leading to death with no apparent cause other than vascular origin[3].

The 24 hours threshold in the definition excludes transient ischemic attacks (TIA).

Stroke includes a number of syndromes with differing etiologies, epidemiology, prognosis and treatment. These are listed in the WHO's international classification of diseases (ICD – 9th revision).

a. Sub arachnoid haemorrhage
b. Cerebral haemorrhage
c. Cerebral thrombosis or embolism
d. Occlusion of precerebral arteries
e. Transient cerebral ischemia of more than 24 hours
f. III defined cerebrovascular disease (i.e., underlying pathology in brain is not determined.

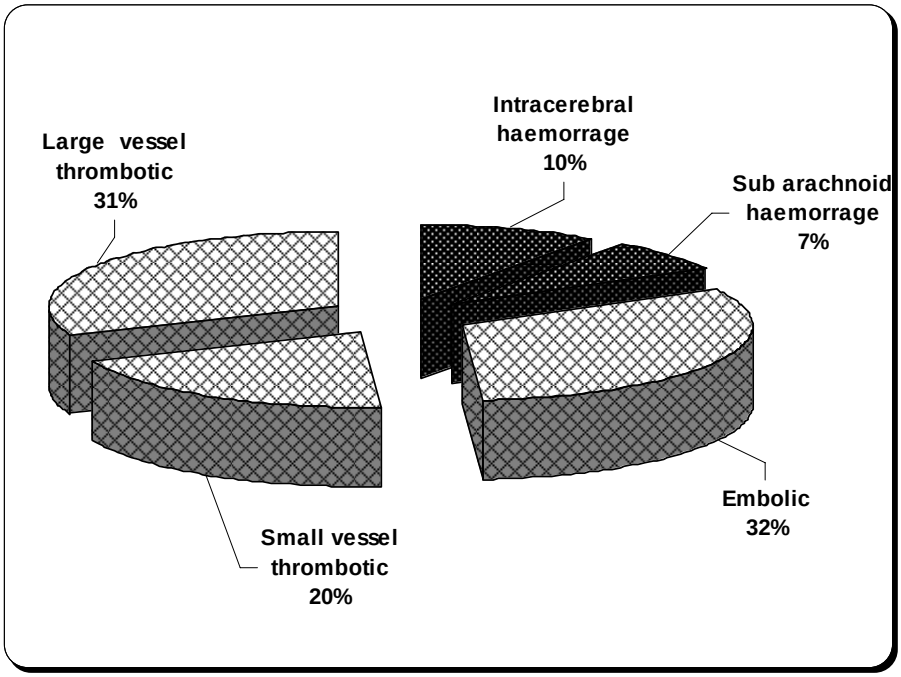
Stroke is a world wide health problem making an important contribution to morbidity, mortality and disability in developed as well as in developing countries.

Stroke is of 2 types, ischemic and hemorrhagic . 83% of stroke is due to ischemia, while hemorrhagic stroke is only 17%[4] (Fig. 1).

Cerebral thrombosis is usually the most frequent form (about 50%) of stroke encountered in clinical studies, though there are substantial differences in frequency from place to place. Cerebral embolism comes next forming 32% of stroke.

Cerebral ischemia is caused by a reduction in blood flow that lasts for a several seconds to few minutes. Neurologic symptoms manifest within 10 sec. because neurons lack glycogen and suffer rapid energy failure. This cerebral ischemia or infarction is usually caused by thrombosis of the cerebral vessels themselves or by emboli from a proximal arterial source or the heart.

Fig.1 : Types of cerebrovascular accident



The causes of ischemia-infarction are:

Ischemic Stroke (83% of stroke)

a. Thrombotic 51%

It consists of 2 sub categories :

(i) Large vessel thrombosis - 31%

(e.g. carotid, middle cerebral, basilar arteries)

(ii) Small vessel thrombosis - 20%

(Lacunar stroke)

(e.g. lenticulostriate, basilar penetrating, medullary)

b. Embolic – 32%

PATHOPHYSIOLOGY OF CEREBRAL ISCHEMIA

The brain is an obligatory aerobe. It derives its energy from the oxidative metabolism of glucose. There are only negligible stores of glucose in the brain. So when the cerebral blood flow falls and the brain becomes ischemic a series of functional and neurophysiological changes, which are dependant on the oxidative metabolism of glucose to provide energy in the form of ATP occurs at various thresholds of flow[5].

The normal cerebral blood flow (CBF) in man is 50ml/100 gms of brain/min. Using positron Emission Tomography, the cerebral energy metabolism is measured as cerebral metabolic rate of oxygen ($CMRO_2$) and of glucose (CMR glu). It has also studied

that the oxygen extraction fraction (OEF) remains the same throughout the brain[6]. Therefore in resting normal human brain, the CBF is a reliable reflection of $CMRO_2$.

In ischemia when CBF falls below about 20 ml/100 gm/min[6], the oxygen extraction fraction becomes maximal and the $CMRO_2$ begins to fall. Infact a high OEF is only seen early after acute ischemic stroke, in the first day or so.

If flow is restored, functional recovery is still possible. At this stage, lactate production increases due to ineffective anaerobic metabolism of glucose. The pH falls and ATP synthesis is impaired. As flow falls further, energy – dependent functions of the cell membranes becomes progressively affected. Water, sodium and chloride enters the cells. Calcium also enters and Potassium (k+) leaks out[7]. Cellular transport mechanisms and neurotransmitter systems fail. Certain potentially neurotoxic transmitters are released such as L-glutamate. The oxygen radicals and lipid peroxides are formed which damage the cell further[8]. Neurons start releasing PAF, (Platelet Activating Factor) which may be neurotoxic.

When the blood flow falls further less than 10ml/100gm/min, infarction occurs and even if flow is restored function does not recover. At this stage, the $CMRO_2$ and CBF is low and OEF may be low indicating the CBF is in excess of requirements for the low

metabolic demands of the infracted tissue. It is called luxury perfusion[9]. In absolute luxury perfusion, CBF is increased which is termed as hyperperfusion.

The consequences of the fall in CBF depend not just on the depth of ischemia, but also on its duration. In focal ischemia, flow is almost never reduced to zero because of the collateral blood supply which is therefore, a further factor in determining the metabolic consequences. The local CBF may also be influenced by the development of cerebral edema and raised intracranial pressure. Acid metabolites and the increasing extracellular potassium concentrations cause vasodilatation. Vasoconstrictor prostaglandins are released from aggregating platelets and damaged cell membranes.

Blood viscosity and aggregation of formed elements slow the microcirculation and eventually thrombosis. The metabolic consequences of ischemia may be exacerbated in the presence of high prevailing glucose concentration. But the worst outcome may be related to the hyperglycaemia of stress response and reflect the severity of initial stroke[10]. When the lactate levels are increased, seizures may occur.

Systemic hypoxia (as a consequence of pneumonia etc) and dehydration, increasing the hematocrit and blood viscosity are further exacerbating factors.

Damaged brain may also have impaired responses to $PaCO_2$ and PaO_2 as well as impaired autoregulation and perfusion reserve. This makes the brain very sensitive to any further insults such as systemic hypoxia, hypotension and raised intracranial pressure.

Free Radical damage

Ischemia induced free radical damage is most likely to occur if ischemia is followed by recirculation. This occurs because oxygen radicals are formed when reduced compound which is accumulated during ischemia is reoxidised. However free radical production can occur at relatively low oxygen tension and can be triggered by the accumulation of reduced compounds.

Ischemia promotes the conversion of Xanthine Dehydrogenase (XDH) to Xanthine Oxidase (XO). A rise in calcium may activate proteases which favours this conversion. Whereas XDH activity does not produce reactive oxygen species, the XO reaction is a major source of free radicals during ischemia reperfusion injury.

$$\text{Hypoxanthine} + O_2 \rightarrow \text{Xanthine} + O_2^{-} + H_2O_2$$

$$\text{Xanthine} + O_2 \rightarrow \text{Uric acid} + O_2^{-} + H_2O_2$$

Another source of free radicals is Nitric Oxide. O_2 and No decompose to form toxic peroxynitrate ion (NO_3^-). No synthetase is also stimulated by the rising calcium levels in the ischemic tissue.

Uric acid, its mono-anion urate (at physiological pH values) is traditionally considered to be a metabolic inert end product of purine metabolism in man without any physiological value.

Uric acid is implicated in various pathological conditions such as Gout, Lesch-Nyhan syndrome, Xanthinuria etc. However, this ubiquituous compound has proven to be a selective anti oxidant[11], capable especially of reaction with hydroxyl radicals and hypochlorous acid. It also gets converted to innocuous products (allantoin, allantoate, glyoxalate, urea, oxalate). There is now evidence for such processes not only in vitro in isolated organs but also in human lung in vivo. Urate may also serve as an oxidizable co-substrate for the enzyme cyclooxygenase. The major site of urate production as shown for coronary system is the mircovascular endothelium in isolated organ preparations. Urate is shown to protect against reperfusion damage induced by activated granulocytes and cells known to produce a variety of radicals and oxidants. Intriguingly, urate prevent oxidative inactivation of endothelial enzymes (cyclooxygenase, Angiotensin Converting Enzymes) preserves the ability of the endothelium to mediate vascular dilatation in the face of the oxidative stress. This suggests a particular relationship between the site of urate formation and the need for a biologically potent free radical scavenger and autoooxidant.

Risk factors for cerebral infarction

1. Unmodifiable risk factors
2. Major modifiable risk factors
3. Questionable rare or weak modifiable risk factors.
4. Risk factors predominant in the young.

Risk factors for cerebral infarction

Unmodifiable risk factors	Questionable, rare, or weak modifiable risk factors	Risk factors predominant in the young
Age	AIDS	Mitral valve leaflet prolapse
Sex	Alcohol	Sickle cell disease and other hemoglobinopathies.
Race		Migraine
Family history	Fibrinogen and platelets	Cocaine abuse
Previous stroke	Lipids	Obstructive sleep apnea
----------	Exercise	Intercurrent infection
Major modifiable Risk factors	Hematocrit	Patent foramen ovale
	Water supply	Atrial septal aneurysm
Atrial fibrillation	Anticardiolipin antibodies	System Lupus erythematosus
Hypertension		
Isolated systolic hypertension	Oral contraceptive	
	Pregnancy	
Myocardial infarction	Homocystinuria	
Other heart disease	Diet	
Diabetes mellitus	Socioeconomic status	
Transient ischemic attacks	Season	
Smoking	Claudication	

A. Unmodifiable Risk factors

a. Age

Age is the single most powerful risk factor for cerebral infarction. Since the increase with age is exponential, doubling or tripling with every decade after the fifth[12].

b. Sex

Mortality rates for men are 23% to 115% higher than for women in all countries[13].

c. Race

There is generally a higher incidence of all strokes types and cerebral infarction in blacks[14].

d. Previous stroke

The recurrence rate of cerebral infarction is 10-30%. The first 6 months is the period of highest risk[15]. Hypertension, Diabetes and Smoking increase the risk, while an infarction of undetermined cause is associated with a diminished risk.

2. Modifiable risk factors

a. Atrial Fibrillation

Atrial fibrillation causes 20% of all infarcts and is associated with a relative risk of death from stroke of 12.25[16]. Silent infarcts

are found in 20% more of the population with atrial fibrillation and this is exacerbated by increasing age and left atrial diameter.

b. Hypertension

After age, hypertension is the most powerful risk factor for cerebral infarction. Both systolic and diastolic pressures are important. Sex differences are not prominent in analyses of the effects of hypertension on stroke. Prolonged treatment of diastolic BP to produce a fall of 6 mmHg decreases the stroke risk by 40% and the benefits accrue within 3 years[17].

c. Myocardial infarction

Cerebral infarction occurs in between 1 % and 1.25% of cases within 1 year after myocardial infarction[18]. Transmural infarcts pose a greater risk than subendocardial infarcts. A history of myocardial infarction is also a risk factor for cerebral infarction.

d. Other Heart disease

Cardiac disease in general doubles the risk of stroke. While left ventricular hypertrophy quadruples it, independent of hypertension. Cardiac failure, coronary Heart disease and angina increases the risk of cerebral infarction.

e. Diabetes Mellitus

Though variable, the evidence now supports diabetes as a risk factor for stroke[19]. Impaired glucose tolerance may be a risk factor and an elevated glycosylated hemoglobin may be found in upto 42% patients with cerebral infarcts not previously known to have diabetes.

f. Transient ischemic Attacks

The incidence of stroke increases after TIA. The relative risk of stroke after TIA is 13.4 in the first 12 months and 7 over first 7 years[20].

g. Smoking

Smoking is one of the most important risk factors. There is a dose response relationship, the risk doubling in the heaviest of smokers[18]. In the Framingham study, cessation of smoking removed the additional risk of stroke within 2 years.

h. Alcohol

The effect of alcohol on cerebral infarction has two aspects. These being sudden heavy (binge) drinking and chronic consumption. There is evidence for an association between sudden heavy drinking and the onset of cerebral infarction in young adults[21]. Chronic light alcohol intake is associated with a

decreased risk of stroke. Chronic heavy consumption 180 – 400 g/wk is associated with an increased risk.

i. Lipids

Total cholesterol has a weak association with cerebral infarction. Framingham study suggest a weak correlation between cholesterol and triglycerides and the risk of atherothrombotic brain infarction.

j. Exercise

Lack of exercise may increase the risk of all stroke in women[22].

Minor factors

Soft water has been associated with an increased risk (7%) of death from stroke according to death certificates.

Anti CardioLipin antibodies are associated with increased risk for cerebral infarction.

Homocystinuria is a recognized high risk factor for stroke.

Acquired Immuno Deficiency Syndrome (AIDS) is a risk factor for infarction. The precise mechanism is unknown, but an associated CNS infection typically with Cryptococcus species, tuberculosis or varicella Zoster is implicated in half of the cases.

Pathophysiology of ischemic stroke subtypes

Cerebral infarction is not a single disease and the differentiation of several clinical, pathophysiologic and etiologic subtypes may be critical for adequate management of patients.

The most common mechanisms of ischemic stroke is thrombosis and embolic, either from an atheromatous arterial lesion (artery to artery thromboembolism) or from the heart (cardio embolism). Less commonly, in situ occlusion of an extra cranial or a cerebral artery may be incriminated in the absence of embolism.

- First, when the occluded artery is a small perforating branch without collateral supply i.e (lacunar infarct.)[23]
- Second, when large-artery occlusion may produce hemodynamic failure in the corresponding territory because of lack of functioning anastomoses (Hemodynamic infarction).
- Finally, abnormalities of the blood, itself may lead to ischemic stroke [(eg) coagulation disorders, hypervisocity, anaemia, leukemia and related disorders].

Intracranial atherosclerosis play a major role in Asians and to a lesser extent in blacks. In whites, extracranial atherosclerosis causes artery to artery embolism. However this distinction is valid mainly for anterior circulation. While recent studies have shown that intracranial vertebral artery or basilar artery atherosclerosis is also an important cause of posterior circulation infarcts[24].

MIDDLE CEREBRAL ARTERY – SUPERFICIAL TERRITORY INFARCTS

Superficial branches of the middle cerebral artery (MCA) originate distal to the origin of lenticulostriate arteries. As they course in the subarachnoid space, they are called pial branches. They supply the cortical, subcortical territory of the MCA after the MCA trunk divide in to two (upper and lower) or three (Upper, middle and lower) divisions which in their turn divide into several branches.

MCA pial territory infarcts may be partial when only a distal branch is occluded, or they may be rather large when the occlusion is more proximal at the level of the MCA bifurcation or trifurcation and the collateral system is not adequate. Because one characteristic of the pial artery network is to have extensive anastomoses, multiple distal emboli are necessary.

The presumed cause of embolism is large-artery disease (>50%) internal carotid artery (ICA) or MCA stenosis or occlusion in one third of the patients and cardiac disease in one quarter of the patients. Interestingly, potential cardiac sources of embolism are particularly common with infarcts in the territory of the lower division of the MCA which are also associated with more disability than infarcts in the territory of the upper division.

Because most of the frontal, temporal and parietal lobes are supplied by the MCA pial branches, the neurologic picture may be variable according to the location of the infarct.

INFARCTS IN THE TERRITORY OF THE DEEP PERFORATORS FROM THE CAROTID SYSTEM

In contrast to the pial artery network, the deep perforators from the distal ICA or the MCA trunk are terminal branches that perforate the basal part of the cerebral hemispheres. For that reason, occlusion of one or several perforators is always associated with an infarcts usually small in the corresponding territory. These small deep infarcts are often called 'Lacunar', but it should be remembered that lacunar may be caused by non ischemic processes such as small hemorrhage or non ischemic dilatation of periarteriolar space.

It is widely accepted that lacunar infarcts are usually due to in situ occlusion of the corresponding small perforator by a micro atheromatous or lipohyalinotic process associated with chronic arterial hypertension. This assumption appears correct for very small lacunar infarcts (<0.3 – 0.5cm) associated with occlusion of one single perforator but these infarcts are usually asymptomatic. Although small artery disease probably remains a leading etiology, in larger (0.5 – 1.5 cm or larger) and symptomatic small deep infarcts, other potential causes may also be considered, since more

than one third of these patients may have a potential cardiac source of embolism or large artery disease (>50%) ICA stenosis or occlusion, often in the absence of concomitant hypertension.

Embolism to the MCA trunk is a particularly common cause of complete lenticulostriate territory infarction (known as large striate capsular infarcts or extended infarcts of the lentiform nucleus), by occluding the leticulostriate arteries at their origin while collateral circulation explains sparing of the superficial pial territory.

Clinical manifestations are largely dependent on the size of infarct. The larger infarcts may produce dysfunction not markedly different from superficial MCA territory infarcts. Smaller infarcts have often been linked to isolated contralateral motor or sensory disturbances (lacunar syndromes).

The classic lacunar syndrome are:

1. Pure motor hemiparesis from an infarct in the posterior limb of the internal capsule or basis pontis, the face arm and leg are almost always involved.
2. Pure sensory stroke – from an infarct in the ventro lateral thalamus.
3. Ataxic hemiparesis – from an infarct in the base of the pontis.

4. Dysarthria and a clumsy hand or arm due to infarction in the base of the pons or in the genu of the internal capsule.

5. Pure motor hemiparesis with motor or Brocas aphasia due to thrombotic occlusion of a lenticulostriate branch supplying the genu and anterior limb of the internal capsule and adjacent white matter of the corona radiata.

ANTERIOR CEREBRAL ARTERY INFARCTS

Although the ACA originates from the carotid system at the same level as the MCA, ACA territory infarcts are between 20-30 times less common than MCA territory infarcts[25]. However, etiologic patterns do not differ between MCA territory infarcts.

Infarcts in the territory of Heubner's artery or in the territory of the anterior striate branches are usually discussed together with lenticulostriate infarcts in general.

In ACA, pial territory infarcts, the association of crural hemiparesis, mutism at onset, transcortical motor aphasia, frontal tasks impairment, mood disturbance, incontinence, grasp reflex and unilateral left apraxia may help to localize the infarct before Computed Tomography or magnetic resonance Imaging, but proportional (arm-leg-arm) hemiparesis or hemisensory defect, hemineglect or confessional state may be misleading. Simultaneous bilateral ACA territory infarction may occur in

relation to a common origin of both ACA territory infarction may occur in relation to a common origin of both ACAs. Akinetic mutism with incontinence and bilateral grasp reflex is suggestive of this type of infarct, which is uncommon (<10%).

BORDER ZONE CEREBRAL INFARCTS

Infarction may develop at the level of the collateral border zone between two main pial arterial territories. Those extra territorial infarcts are commonly called watershed or distal field infarcts. They usually occur between the ACA and MCA territories anterior water shed infarcts or between the MCA and posterior cerebral artery (PCA) territories – posterior water shed infarcts.

In anterior water shed infarcts, hemiparesis, predominating in the lower limb, with transcortical motor aphasia when lesion is on the left, is the most common neurologic finding when the infarct predominates in the subcortical white matter, mimicking ACA territory infarction. However, when the infarct is limited to the cortex, proximal brachial hemiparesis is present because junction of the arm-shoulder representation on the motor strip, thus in bilateral anterior watershed cortical infarcts, a picture bi-brachial paralysis (man-in-the -barrel) may occur.

Posterior watershed infarcts yield a neurologic picture that is similar to that of posterior MCA pial territory infarcts except for a more common occurrence of transcortical sensory aphasia.

Bilateral watershed infarcts often have a symmetrical pattern. They usually develop in relation to episodes of severe hypotension, cardio circulatory distress, prolonged hypoxemeia or bilateral severe carotid disease[26]. Venterolateral watershed infarcts are also associated with some degree of hemodynamic failure (hypotension, bradycardia, high hematocrit level) in patients with ipsilateral carotid occlusion or tight stenoses. They are good examples of hemodynamic infarcts, though mircroemboli may account for some border zone infarcts.

An infarction between the deep and superficial (pial) territories of the MCA is uncommon. It is called a sub cortical watershed[26]. Hemiparesis with or without hemisensory disturbance is the most common neurologic disturbance in these infarcts.

POSTERIOR CEREBRAL ARTERY - SUPERFICIAL TERRITORY INFARCTS

The superficial (pial) branches of the PCA include the hippocampal, medial temporo – occipital, splenial, internal occipital and calcarine branches. The posterior choroidal branches have an internal temporal pial network, but they are usually considered with the deep branches of the thalamus. Infarcts limited to the territory of just one branch of the PCA are the most commonest type of PCA pial territory infarction (uniterritorial), often involving the calcarine artery territory. Isolated mediotemporal involvement

is rare. The most common biterritorial infarct combines calcarine and internal occipital arteries territory involvement.

The neurologic manifestation are dominated by visual symptoms, which may be simple (hemianopia) or complex (alexia, achromatopsia, agnosia, visual memory impairment.)

In pathologic series, PCA infarction is often due to compression by edema during temporal lobe herniation. In a clinical setting the etiology is usually embolic, mainly from the heart, vertebro basilar atherosclerosis.

THALAMIC INFARCTS

The arterial supply to thalamus may be divided into four main groups.

1. The paramedian or thalomo perforate branches from the P_1 segment of the PCA.
2. The infero lateral or thalamo geniculate branches from the P_2 segment of the PCA.
3. The posterior choroidal arteries (one lateral and one medial group) from the P2 segment of PCA.
4. The tuberothalamic or polar branches originate from posterior communication artery.

The etiology of thalamic infarct is varied. Small vessel disease associated with hypertension or diabetes accounts for not more than one third of the cases, while cardio embolism and artery – to – artery embolism accounts for atleast 25% to 30%. Other causes such as arteritis, migraine and so on may also be responsible. Usually simultaneous occlusion of several perforators (from embolism) may be necessary to lead to infarct.

BRAIN STEM INFARCTS

Mid brain, pontine and medullary infarcts usually develop in characteristic territories in relation to a stereotyped blood supply system which includes (from medial to lateral side) paramedian perforating branches and short circumferential arteries directly from the basilar artery and large circumferential arteries, which are infact the three cerebellar arteries:

1. The Superior Cerebellar Artery (SCA)
2. Anterior Inferior Cerebellar Artery (AICA) and
3. Posterior Inferior Cerebellar Artery (PICA) and supply the dorsal brain stem as well as their cerebellar territory

Most of the clinically relevant brain stem infarcts involve the paramedian and lateral (short circumferential branches) territories. Thus, they may be associated with small – vessel disease (lacunar infarction) but also with basilar artery (for the pons and mid brain) or vertebral artery (for the medulla) disease

that obstructs the mouth of these small arteries (branch disease). Large embolism, which may stop more proximally in the basilar artery, lead to large infarcts not limited to the brain stem. The neurologic manipulations caused by brain stem infarcts are multiple.

CEREBELLAR INFARCTS

1. PICA Territory Infarcts

PICA territory infarcts are the most common type of symptomatic cerebellar infarcts. Most cases seem related to atheromatous occlusion of the vertebral artery, less commonly the PICA itself.

2. AICA Territory Infarcts

AICA territory infarcts are the less common type of cerebellar infarcts. Infarcts in the lateral part of the lower pons is usual in association with cerebellar involvement. Contrary to PICA and SCA territory infarcts, cardioembolism seems to be an uncommon cause. Atherosclerosis plays a major role.

3. SCA Territory Infarcts

In SCA territory infarcts, clinically relevant brain stem (Mid brain) involvement is less common than in AICA territory infarcts, where cardio embolism is a classic cause.

Other Cerebellar Infarcts

Large cerebellar infarcts are usually MCA territory infarcts in patients with AICA aplasia. They are typically responsible for a rapid deterioration, tonsillar herniation and death in the absence of surgical intervention.

Watershed cerebellar infarcts may occur at the border zone between PICA, SCA and AICA territories. Their clinical diagnosis is controversial since the overlap of the cerebellar arteries may be particularly variable.

INVESTIGATIONS

COMPUTED TOMOGRAPHY (CT)

The role of computed Tomography in the diagnosis of cerebral infarction is well established. CT can distinguish between an ischemic bland-non haemorrhagic stroke, haemorrhagic infarction and primary intracerebral Haemorrhage[27].

In the clinical setting of a transient ischemic attacks (TIA) the CT scan is usually normal, however the detection of white matter or capsular hypodensity (chronic ischemic change) establishes the presence of underlying vascular disease.

The classic neuropathologic process that occur during the evolution of an infarction is well reflected by the CT scan. The

radiologic imaging characteristics are divided in to four stages and are dependant on the time from the onset of ictus. These stages are divided into

1. Hyperacute less than 24 hrs
2. Acute 24 hrs – 7 days
3. Subacute 8-21 days
4. Chronic More than 21 days

MAGNETIC RESONANCE IMAGING (MRI)

Image contrast with magnetic resonance imaging is dependent on three tissue variables. T1 – Relaxation time, T2 – Relaxation time and Proton density.

Ischemia one hour after the event can be detected by MR imaging. MRI reliably documents the extent and location of infarction in all area of the brain, including the posterior fossa and cortical surface. Diffusion weighted imaging is more sensitive for early brain infarction. Magnetic Resonance angiography is highly sensitive for extracranial internal carotid plaque as well as intracranial stenosis of large vessels. MRI proves superior information compared with CT in nearly every case of stroke.

CEREBRAL ANGIOGRAPHY

Conventional X-Ray cerebral angiography is the "gold standard" for identifying and quantifying atherosclerotic stenoses

of the cerebral arteries and other pathologies. Recent studies have documented that intra arterial delivery of thrombolytic agents to patients with acute MCA infarct can effectively recanalize vessels and improve clinical outcomes.

Baseline tests for most ischemic stroke patients

Sl. No	Investigation	Treatable disorders detected
1.	Full blood count	Anaemia, Polycythaemia, leukemia, thrombocytopenia
2.	ESR	Vasculitis, infective endocarditis hyperviscosity
3.	Plasma glucose	Diabetes, hypoglycaemia
4.	Plasma cholesterol	Hyper cholesterolemia
5.	Syphilis serology	Syphilis, anti cardiolipin antibody
6.	Urine analysis	Diabetes, renal disease
7.	Electro Cardiogram	LVH, arrhythmias, conduction block, myocardial ischemia or infarction

PREDICTION OF STROKE OUTCOME

The outcome of stroke is influenced by many factors. Among them, some of the most important are demographic factors such as age, sex, etc, risk factors, clinical examination findings, laboratory tests and imaging. These factors provide important insight regarding outcome.

1. DEMOGRAPHIC FACTORS

a. Age

It is one of the major factors which can negatively influence the outcome. Poor outcome in old age is due to increased frequency of secondary complications such as pneumonia, bed sores etc.

b. Gender

Stroke in males poses poor outcome. Endogenous estrogens in females is found to be neuroprotective and has flow preserving effects.

2. RISK FACTORS

Previous stroke and atrial fibrillation causes more disability and associated with increased mortality[16].

3. CLINICAL FINDING

a. Level of Consciousness and Gaze Deviation

A decrease in the level of consciousness and presence of gaze deviation indicates poor outcome.

b. Blood Pressure

Systemic hypotension can cause a fall in cerebral blood flow which may cause a decreased blood flow to the infracted area.

A rise in BP may have long term adverse effects on the blood brain barrier. Under severe hypertension the infracted area can go for haemorrhagic transformation.

c. Temperature

A two fold increase in the relative risk for poor outcome in stroke is seen with every 1^{o}c rise of temperature. This effect may be due to excitotoxic neurotransmitters.

COMPLICATIONS

The most important local complication of cerebral infarction is the development of cerebral oedema, which impairs, possibly only temporarily, local blood flow and neuronal function over a wider area than just the infarct and, if extensive, causes transtentorial herniation. There are a number of general complications of acute paralysis which include bronchopneumonia, particularly if consciousness or swallowing are impaired; venous thromboembolism; pressure sore and septicaemia; urinary infection, particularly if catheterization is necessary, and eventually uraemia; contractures in spastic limbs; frozen shoulder; cardiac rhythm disturbances; and mood disorder (Table). Death in the first week is almost always due to the infarct itself and the effects of cerebral oedema, but later it is more often due to one of the general complications, particularly pneumonia.

Table

General complications of stroke

Respiratory	Pneumonia Inhalation Pulmonary embolism
Cardiovascular	Myocardial infarction Cardiac failure Cardiac arrhythmia Neurogenic pulmonary oedema
Infections	Pneumonia Urinary track infection Skin Septicaemia
Metabolic	Vomiting Dehydration Electrolyte imbalance Hyperglycaemia Renal failure
Mechanical	Spasticity Contractures Malalignments/subluxation/frozen shoulder Falls and fractures Osteoporosis Ankle swelling Peripheral nerve pressure palsies
Others	Pressure sores Depression, anxiety, apathy Epileptic seizures Deep venous thrombosis Acute gastric ulceration Incontinence of urine/faeces

Course and Prognosis

When the patient is seen early in the course of cerebral thrombosis, it is difficult to give an accurate prognosis. No rules have yet been formulated that allow one to predict the course with confidence. A mildparalysis today may become a disastrous hemiplegia tomorrow, or the patient's condition may worsen only temporarily for a day or two. In basilar artery occlusion, dizziness and dysphasia may progress in a few days to total paralysis and deep coma.

The progression of the stroke is mostly often due to increasing stenosis of the involved artery by mural thrombus. In some instances, extension of the thrombus along the vessel may block side branches and hinder anastomotic flow. Embolic particles from the site of an incompletely thrombosed artery (artery-to-artery embolism) may precipitate an abrupt change. Sometimes a completely thrombosed artery or an artery whose lumen is narrowed by a dissecting aneurysm can be the source of an embolus to more distal branches after a period of several days.

Several other circumstances influence the immediate prognosis in cerebral thrombosis. In the case of very large infarcts, swelling of the infracted tissue may occur, followed by displacement of central structures, tentorial herniation, and death of the patient after several days. Smaller infarcts of the inferior surface of the

cerebellum may cause a fatal foramen magnum herniation. Milder degrees of swelling and increased intracranial pressure may cause apparent progression for 2 to 3 days but do not prove fatal. In extensive basilar infarction associated with deep coma, the mortality rate approaches 40 percent. If coma or stupor is present from the beginning, survival is largely determined by the success in keeping the airway clear, controlling brain edema, preventing aspiration pneumonia, and maintaining fluid and electrolyte balance. Respiratory and urinary infections are constant dangers: once they begin, there is usually a rapid decline in the patient's condition as body temperature rises. With smaller thrombotic infarcts, the mortality is 3 to 6 percent.

Characteristically, the paralyzed muscles are flaccid in the first days or weeks following a stroke; the tendon reflexes are usually unchanged but may be slightly increased or decreased. Gradually spasticity develops, and the tendon reflexes become brisker. The arm tends to assume a flexed adducted posture, and the leg an extended one.

Function is rarely if ever restored after the slow evolution of spasticity. Conversely, the early development of spasticity in the arm or the early appearance of a grasp reflex may presage a favourable outcome. Bowel and bladder control usually returns; sphincteric disorders persist in only a few cases. Often the hemiplegic limbs are at first tender and ache on manipulation.

Nevertheless, physiotherapy should be initiated early in order to prevent pscudocontracture of muscles and periarthritis at the shoulder, elbow, wrist, knuckles, knee, and ankle.

Recurrent convulsive (epileptic) seizures are relatively uncommon sequelae of thrombotic strokes in comparison to embolic cortical infarcts, which are followed by recurrent focal or generalized seizures in more than 20 percent of patients.

Many patients complain of fatigability and are depressed, possibly more so after strokes that involve the left frontal lobe (Starkstein et al.). The explanation of these symptoms is uncertain; some are expressions of a reactive depression. Only a few patients develop serious behaviour problems or are psychotic after a stroke, but paranoid trends, ill temper, stubbornness, and peevishness are common.

Finally, in regard to prognosis, it must be mentioned that having had one thrombotic stroke, the patient is at risk in the ensuing months and year of having a stroke at the same or another site, especially if there is hypertension or diabetes mellitus. When multiple infarcts occur over a period of months or years, a dementia may develop, in addition to focal cerebral deficits. As a group these cases are referred to as multi-infarct dementia. In some of these cases, the major lesions involve the white matter with relative sparing of the cortex and basal ganglia. This type of lesion is often

referred to as a Binswanger's subcortical encephalopathy, which is equated with multiple white matter infarcts and lacunes. The part of the white matter that are destroyed have been shown to lie in the border zones between the penetrating cortical and basal ganglionic arteries.

TREATMENT

Medical treatment has a greater role to play than vascular surgery to alter the immediate outcome after cerebral infarction. In theory the reduction of cerebral oedema by mannitol, glycerol should be useful, but with regard to dexamethasone there have been no adequate clinical trials. Thrombolysis causes intracerebral haemorrhage and this risk may not be out weighed by the potential benefit, if any. Aspirin is currently being used. Heparin has been recommended for stroke-in-evolution, although there have been no convincing trails and, since some cases may be due to haemorrhage into infarcted brain, this treatment is not to be recommended. It is important to remember that there are many other reasons for stroke patients to deteriorate and some are potentially reversible.

Table

Causes of neurological deterioration after stroke

Local	Extension of thrombus Recurrent embolism Recurrent haemorrhage Haemorrhagic transformation of the infarct Cerebral oedema Brain shift and herniation Hydrocephalus Epileptic seizures
General	Hypoxia (pneumonia, pulmonary embolism, cardiac failure Hypotension (cardiac failure, cardiac arrhythmia, Septicaemia, pulmonary embolism, dehydration, Pneumonia, drugs, bleeding or perforated peptic ulcer) Infection (chest, urine, septicaemia) Dehydration Hyper-or hypoglycaemia Sedatives/hypnotics

The complications of cerebral infarction are often preventable and treatable. Chest physiotherapy and care of the airway, particularly in unconscious patients and those with difficulty in swallowing, will reduce the risk of pneumonia which, if it occurs, can be treated with antibiotics. Occasionally intubation and

tracheostomy are needed in patients who cannot protect their airway due to impaired brain-stem reflexes, but who are otherwise expected to have a reasonably good prognosis. Nasogastric tube feeding is used for adequate hydration and electrolyte balance in patients who cannot swallow, and later for feeding if necessary. Good nursing should prevent pressure sores. Early physiotherapy will reduce the risk of contractures, pain, and stiffness in hemiplegic limbs and leads naturally on to active physical rehabilitation. Urinary catheterization is often avoidable in males for whom an appliance is a better alternative, but in females it may be necessary so that the skin can be kept dry to reduce the chance of pressure sores. Cardiac arrhythmias should be treated on their merits, but are not normally a problem. Since cerebral infarcts can become haemorrhagic, it is uncertain whether deep venous thrombosis in the legs and pulmonary embolism should be prevented, or even treated, with antithrombotic drugs, but the benefit of high –does heparin followed by oral anticoagulation for major pulmonary embolism probably outweighs the risks. Epilepsy, if it occurs, should be treated in the usual way.

MATERIALS AND METHODS

Setting

The work was carried out in the medical wards of Government General Hospital, Chennai affiliated to Madras Medical College, Chennai.

Study design

Cross Sectional, analytical hospital based study.

Period of study

The study was carried out from November 2006 to May 2007.

Ethical Approval

The work was carried out after approval from ethical committee of Government General Hospital, Chennai (copy enclosed).

Sample size

Study group (Stroke cases)	:	102
Control group	:	40

Methodology

Study Group

Government General Hospital is a tertiary care institute and referral centre for patients from all over South India.

The stroke patients admitted within the above period and who satisfied the set criteria were included. The number of patients in the present study group was 102.

INCLUSION CRITERIA

1. **Patients with stroke as defined by WHO criteria**

   Rapidly developing clinical signs of focal or global (coma) neurological deficit lasting more than 24 hrs or leading to death with no apparent cause other than vascular origin.

2. All patients who presented within 48 hours of onset of stroke and who gave informed consent to participate in the study were included.

EXCLUSION CRITERIA

1. Patients with Sub arachnoid haemorrhage, extradural haemorrhage subdural haemorrhage and intra cerebral haemorrhage were excluded by CT.
2. Patients with previous history of TIA/RIND.
3. Patients with gout.

4. Patients who were alcoholics.
5. Patients taking drugs causing hyperuricaemia.

   eg. With the following drugs like

   - Loop diuretics
   - Anticancer drugs (Cisplatin, cyclosporine, cyclophosphamide)
   - ATT (Pyrazinamide, Ethambutol)
   - Aspirin, Pentamidine, Theophylline, ketoconazole,
   - Levodopa, isotretinoin.

6. Patients with previous history of coronary vascular events
7. Kidney disease
8. Patient on medication to reduce oxidant levels
9. Hypothyroidism
10. Inflammatory diseases
11. Steroid therapy

Control group

People without stroke who satisfied the above exclusion criteria and matched for age, gender, diabetes, hypertension were taken as control. The number of controls in the present study was 40.

Data Collection

The socio demographic, clinical, laboratory parameters and outcome data were collected.

Socio demographic data included age of the patients, sex, area of residence, income, diet and time of hospitalisation after stroke.

Clinical data included recording of vital parameters, fundus examination, the type of stroke, conscious level of the patients assessed by the glasscow coma scale and complete neurological examination.

Laboratory parameters included complete blood count, renal function tests, fasting blood sugar and CT Scan brain.

The serum uric acid level was measured in the stroke patients and control by the uricase method.

The test was done in the Biochemistry Lab at Government General Hospital, Chennai.

Laboratory assessment of Uric acid (Uricase method)

A reagent kit is available at the central biochemistry laboratory, Government General Hospital. This reagent kit is for quantitative estimation of uric acid in serum or plasma.

Principle

$$\text{Uric acid} + O_2\text{-}2H_2O \xrightarrow[\text{Uricase}]{} \text{Allantoin} + CO_2 + H_2O_2$$

$$2H_2O_2 + 4 \text{ Amino antipyrine} + \text{DHBS} \rightarrow \text{Chromogen} + 4H_2O$$

Uric acid in serum is oxidized by uricase to allantoin and hydrogen peroxide. Hydrogen peroxide thus generated is acted upon by peroxidase and oxidizes the chromogen (4 amino antipyrine + DHBS) to a red coloured compound which is read at 520 nm (490-550 mm) or with a green filter. The colour intensity at 520 nm is proportional to the concentration of the uric acid in the sample.

The reagent kit is provided with three solutions namely

1. Uric acid (enzyme, chromogen)
2. Uric acid (buffer)
3. Uric acid (standard 5mg/dl)

This reagent is for invitro diagnostic use.

Preparation of working solution

A working solution was prepared by dissolving the content of vial labeled I uric acid (enzyme) with the quantity of 2. Uric acid (buffer). The two solutions were mixed gently.

Specimen Collection

Fresh clear serum with no hemolysis is the specimen of choice. However, plasma collected from blood with heparin as an anti coagulant was used in the present study.

Procedure

The sample and working solution were brought to room temperature prior to use.

25 µ1 of the sample is mixed with 1 ml of working reagent. The solution is incubated at 37°c for 5 min or 10 min at room temperature. The wavelength of the solution and that of the blank reagent solution are compared at 520 nm or with green filter.

Another procedure for 2.5 ml curette capacity is

	Blank	**Standard**	**Test**
Working reagent	2.5 ml	2.5 ml	2.5 ml
Standard	-	0.05 ml	-
Sample	-		0.05 ml

The mixed solution was incubated for 5 min at 37°c and read absorbance of the test and standard against reagent blank at 520 nm or with green filter.

Calculations

$$\text{Uric acid concentration mg/dl} = \frac{\text{Absorbance of test}}{\text{Absorbance of Standard}} \text{ X } 5$$

To convert uric acid concentration from mg/dl to µmoles/L, the following equation was used

µmoles/L = 59.5 X mg/dL

µmoles/L = 0.0595 X mg/L

Definitions

Diabetes Mellitus： People whose fasting blood sugar more than 126 mg/dL and known patients with type 2 Diabetes mellitus on oral hypoglycaemic drugs or insulin therapy.

Hypertension： Patients with BP 140/90mm/Hg on 2 separate occasions, each on different days and known patients of hypertension on treatment.

Serum uric acid level was measured in the stroke cases before they were treated with antiedema measures and aspirin.

Supportive care including physiotherapy was given. Neurologist opinion was obtained if needed.

Outcome assessment

These patients were followed up for a period of 2 weeks in the hospital and the outcome in them assessed by Glassgow outcome scale[28] at the end of 2 weeks.

GLASGOW OUTCOME SCALE

1. Indicates **death**
2. **Vegetative state** (patient is unable to interact with environment)
3. **Severe disability** (patients is unable to live independently but can follow commands)
4. **Moderate disability** (patients is capable of living independently but unable to return to work or school).
5. **Mild or No disability** Patient can return to work or school.

Scale 4 & 5 - Favourable outcome (good outcome)

Scale 1,2 & 3 - Unfavourable outcome (poor outcome)

The data were entered in microsoft excel software and analysed using SPSS 2007 statistically.

RESULTS

GENDER

In the 102 stroke patients, 66 were males and 36 females. The mean serum uric acid level in males (5.76 mg/dL) was higher than in females (5.47 mg/dL). No significant association was found between gender and uric acid level (P = 0.370) as shown in Table No. 1.

TABLE 1 : SERUM URIC ACID LEVEL BETWEEN MALES & FEMALES IN THE STROKE CASES

S. No.	Gender	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	Males	66	5.76	1.62	-0.347	0.370
2.	Females	36	5.47	1.40	0.923	

AGE

The age of stroke patients varied from 30 to 70 years. Mean age of the study group was 56.72 ± 1.89. The serum uric acid level was compared between age groups of > 50 and ≤ 50 years in the control and stroke cases.

Control Group

In the control above 50 years had uric acid level more than people ≤ 50 years. But statistically it was not significant (P = 0.055) as shown in Table No. 2.

TABLE 2 : SERUM URIC ACID BETWEEN THE AGE GROUPS ≤ 50 YEARS AND > 50 YEARS AMONG CONTROL

S. No.	Age	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	≤ 50 years	19	4.050	0.7557	-0.3771	0.055
2.	> 50 years	21	4.105	0.5862	0.4871	

Stroke Cases

Similarly within the stroke cases, uric acid level was compared between the age groups > 50 years and ≤ 50 years.

In the stroke patients > 50 years had mean uric acid level of 5.788 mg/dL while patients ≤ 50 years had mean serum uric acid level 5.238 mg/dL. Statistical no association seen (P = 0.125), as shown in Table No. 3.

TABLE 3 : SERUM URIC ACID BETWEEN AGE GROUPS ≤ 50 YEARS & > 50 YEARS AMONG STROKE CASES

S. No.	Age	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	≤ 50 Years	34	5.238	1.578	-1.260	0.127
2.	> 50 years	68	5.788	1.518	0.1588	

SOCIO ECONOMIC STATUS

On the basis of Kuppusamy socio economic scale, it was found that 95 of the stroke cases belonged to low socio economic group while remaining 7 were of middle socio economic group.

DIET

A detailed questionnaire was used to assess dietary habits of stroke subjects. 97 patients consumed non vegetarian diet while 4 were pure vegetarians. But due to the low socio economic status of the majority, the quantity of non-vegetarian food consumed per week was considerably low.

RESIDENCE

- 54 patients were from rural areas.
- 34 patients resided in semiurban areas
- The remaining 14 patients were from urban areas.

URIC ACID LEVEL AND STROKE

The study group consisted of 102 stroke patients. The mean serum uric acid level in the stroke cases was 5.66 mg/dL with range 4.12 to 7.2 mg/dL. The control group had 40 members. The mean serum uric acid level in the control group was 4.08 mg/dL with range 3.41 to 4.75 mg/dL.

The serum uric acid level of the stroke cases was compared with control group. The stroke cases had increased uric acid level than control with statistically significant association ($P < 0.001$) as shown in Table No. 4.

TABLE NO. 4 : SERUM URIC ACID LEVEL BETWEEN STROKE CASES AND CONTROLS

S. No.	Group	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	Stroke Cases	102	5.66	1.54	-1.214	0.000
2.	Control	40	4.08	0.67	-1.949	

RISK FACTORS

(i) Diabetes

In the study group 33 patients had diabetes and in the control group 11 were diabetics. The serum uric acid level was compared between them.

Diabetics with stroke had elevated uric acid than diabetics without stroke ($P < 0.001$). Statistical association was present as shown in Table No. 5.

TABLE 5 : SERUM URIC ACID AMONG DIABETIC STROKE CASES AND CONTROL

S. No.	Group	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	Stroke Cases	33	5.50	1.59	-0.353	0.009
2.	Control	11	4.15	0.63	-2.350	

Similarly serum uric acid level in diabetics and non diabetics within the stroke cases were compared. The mean uric acid level in diabetics with stroke was 5.74 mg/dL while that of non diabetic stroke patients were 5.49 mg/dL. There is no statistical significance between them (P = 0.467) as shown in Table No. 6.

TABLE 6 : SERUM URIC ACID AMONG DIABETIC AND NON DIABETIC STROKE CASES

S. No.	Risk Factor	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	Diabetics	33	5.74	1.526	0.889	0.467
2.	Non Diabetics	69	5.4970	1.588	0.410	

DIABETES AND OUTCOME

The outcome was compared between the diabetics and non diabetics in the stroke patients.

In the diabetic poor outcome (54.5%) was more common than good outcome (45.5%) but not statistically significant (P = 0.057) as shown in Table No. 7.

TABLE 7 : OUTCOME IN DIABETIC AND NONDIABETIC STROKE CASES

Cases	Outcome		Total
	Good	Poor	
Diabetes	15 (45.5%)	18 (54.5%)	33 (32.4%)
Non Diabetics	45 (65.2%)	24 (34.8%)	69 (67.6%)
Total	42 (41.2%)	60 (58.8%)	102 (100%)

HYPERTENSION

Among the stroke cases, 54 were hypertensive, while in the control 12 were hypertensive. The serum uric acid level was compared between them.

The hypertensive in control had mean uric acid of 4.06 mg/dL while the hypertensive in cases had mean uric acid of 5.71 mg/dL. There is significant association between stroke patients with hypertension and elevated uric acid (P = 0.001) as shown in Table No.8.

TABLE 8 : SERUM URIC ACID AMONG HYPERTENSIVE STROKE CASES & CONTROL

S. No.	Group	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	Cases	54	5.71	1.53	-0.751	0.001
2.	Control	12	4.06	0.59	-2.551	

When the serum uric acid level was compared between the hypertensive and non hypertensive within the stroke cases there was no significant association (P = 0.728) as shown in Table No.9.

TABLE 9 : SERUM URIC ACID AMONG HYPERTENSIVES AND NON HYPERTENSIVES WITHIN STROKE CASES

S. No.	Risk Factor	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	Hypertensive	54	5.71	1.53	-0.503	0.728
2.	Non Hypertensive	48	5.60	1.57	0.717	

SMOKING

In the stroke cases 44 were smokers. Their uric acid level was compared with that of the non smokers among the stroke cases. There was no significant association (P = 0.879) as shown in Table No.10.

TABLE 10 : SERUM URIC ACID AMONG SMOKERS AND NON SMOKERS IN THE STROKE CASES

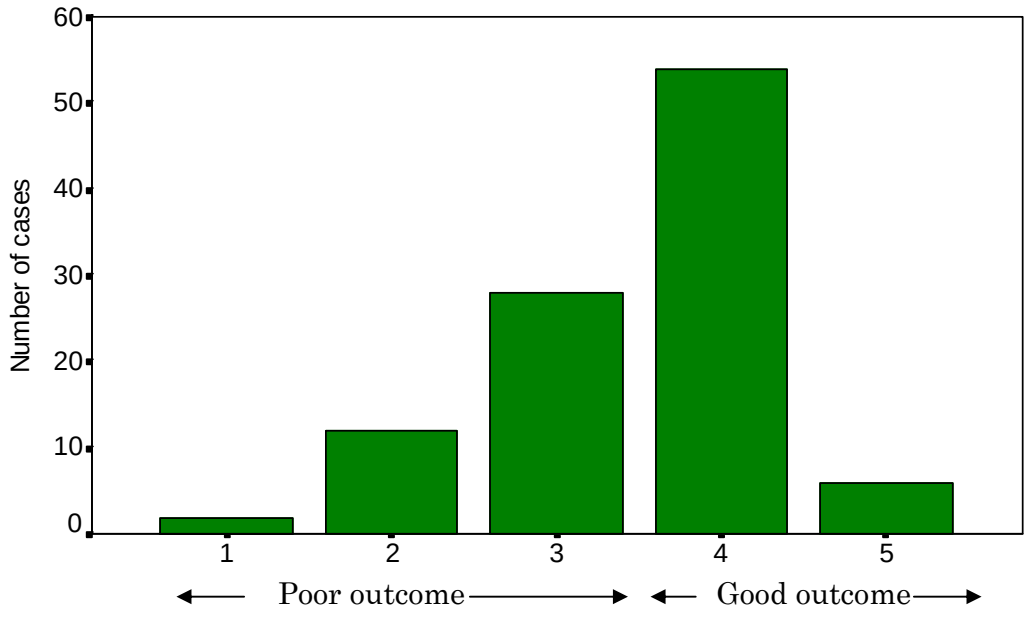
S. No.	Risk factor	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	Smokers	44	5.63	1.58	-0.633	0.879
2.	Nonsmokers	58	5.68	1.52	0.568	

STROKE OUTCOME AND URIC ACID

Of the 102 cases, 91 had middle cereberal artery territory infarct, while 11 had posterior circulation stroke. The outcome was analysed in the stroke patients using glasscow outcome scale. 60 of them had good outcome while 42 had poor outcome as shown in the Figure - 2.

Fig. 2

OUTCOME SCALE IN THE STROKE PATIENTS



Outcome Scale

The serum uric acid level was compared between stroke cases with good outcome and poor outcome.

Mean serum uric acid in the stroke patients with poor outcome (6.41 mg/dL) was higher than that in the stroke patients with good outcome (5.13 mg/dL).

There is statistical association (P value < 0.001) between increased uric acid level and poor outcome as shown in Table No.11.

TABLE 11 : SERUM URIC ACID AMONG STROKE CASES IN RELATION TO OUTCOME

S. No.	Stroke Cases	No.	Mean	SD	C.I.	P value
1.	Good outcome	60	5.13	1.45	0.716	0.001
2.	Poor outcome	42	6.41	1.37	1.845	

The stroke patients without selected risk factors (hypertension, diabetes, smoking) were 38 in the study. Among them, the uric acid level was compared between those with good outcome and poor outcome.

Mean serum uric acid in the stroke patients without risk factors and poor outcome (4.92 mg/dL) was higher than those with good outcome (6.32 mg/dL).

There is a significant association between elevated uric acid level and poor outcome in stroke patients without risk factors ($P < 0.001$) shown in Table No.12.

TABLE 12 : SERUM URIC ACID IN STROKE PATIENTS WITHOUT RISK FACTORS WITH OUTCOME

S. No.	Stroke Cases	No.	Serum Uric Acid Level			P value
			Mean	SD	C.I.	
1.	Good outcome	15	4.92	1.61	4.03 to 5.8	< 0.001
2.	Poor outcome	23	6.32	0.69	5.8 to 6.8	

DISCUSSION

Uric acid which is an end product of purine metabolism has long been considered only in the pathogenesis of gout and uric acid stones. Its anti-oxidant functions and its various role in the pathogenesis of hypertension, cardiovascular and cerebrovascular events are been considered of late. Various studies conducted during recent years on serum uric acid levels in vascular events have proven its prognostic significance.

Uric acid is also been considered as a marker for atherosclerosis. But the exact pathogenesis and whether it is the cause or effect of atherosclerosis remains to be elucidated.

Uric Acid and Gender

The serum uric acid level was compared between male and female stroke patients. Though it was increased in males, statistical association between gender and uric acid was not present. But in a study by Chamorro et al.[29] serum uric acid levels were found to be higher in males.

Age Group

In our study, most of the patients were in the age group of 50 years and above i.e. 76% of patients.

Stroke occurs predominantly in the middle and late years of life[30]. When serum uric acid level was compared between age groups of ≤ 50 years and > 50 years in control and cases, there was no significant association.

Age group of the patients has been found to have no correlation with serum uric acid levels in the present study.

In a study by Milionis et al.[31] elevated uric acid was associated with increased risk of ischemic stroke in individuals above 70 years. Since in the present study, patients older than 70 years were not present, this correlation is not possible.

Uric Acid Level among Control & Stroke Patients

Uric acid levels were found to be significantly higher among patients with stroke than the control in this study. A study by Hozawa A. Folsom et al.[32] also showed increased uric acid levels in patients with ischemic stroke.

Longo Mbenza, et al.[33] in a study among African patients found that uric acid levels were elevated among stroke patients. In a study by Iribarreen, Folsom and Eckfeldt et al., [34] they tried to

find the correlation between uric acid levels and asymptomatic carotid atherosclerosis. They found a positive correlation between the two and that uric acid level can be used to predict future cerebrovascular events.

Uric Acid and Diabetics

In the present study diabetic patients who developed stroke had higher uric acid level than the diabetics in the control group with significant association.

Among the stroke patients no significant difference in uric acid levels was found between diabetics and non diabetics.

Lehto et al.[35] studied uric acid levels in diabetics patients prospectively and showed that it was more elevated in the diabetics who developed stroke.

Diabetics and Outcome

Among the stroke patients, outcome in diabetic and non diabetic was analysed, diabetics had higher percentage of poor outcome (54.5%) than good outcome (45.5%), but statistically no significant association (P = 0.057) was seen. A study by Wang, Lim et al.[36] showed that hyperglycemia increases stroke mortality. In yet another study by Yoon, et al.[37], they found high blood glucose is associated with poor outcome after ischemic stroke. In the present study only 33% of stroke patients were diabetics. So this correlation

was probably not possible. We may need a large multicentered study.

Hypertension and uric acid

Hypertensive patients who developed stroke had increased uric acid level than the hypertensive in the control group with statistical significant association ($P < 0.001$). Among the stroke patients, no significant difference in uric acid level was found between the hypertensive and non hypertensives.

In a study by Verdecchia P and Schillaci et al.,[38] it was proven that there is a definite relation between serum uric acid and essential hypertension.

Theodore R Fields et al.,[38] in his study on uric acid and cardiovascular disease discussed pathogenic role of uric acid in hypertension - 'Chicken and Egg' theory ie., whether uric acid is the cause or effect of hypertension. In his study, he included coronary artery diseases also and found that uric acid has no etiological role in hypertension. His conclusion was that elevated uric acid is secondary to the systemic hypertension.

Elevated serum uric acid in hypertensives can be associated with ischemic stroke. This has been showed in a study by Franeesea Viazzi et al.,[39] who found that cerebrovascular events was higher in hypertensives with increased uric acid level.

Smoking

Smoking was not found to be associated with elevated uric acid levels among patients with stroke in this study.

Angel Chamorro et al.[34] in his study has proven that uric acid levels are independent of smoking. However, associated atherosclerosis can elevate the uric acid levels falsely giving an impression that smokers have elevated uric acid levels.

Uric Acid and outcome in stroke patients

Elevated uric acid was found to be significantly associated with poor outcome among the stroke patients in the present study.

To eliminate the potential bias created by risk factors (diabetes, hypertension, smoking), the uric acid level was analysed among stroke patients without these selected risk factors and compared with outcome. It was found that uric acid was still an independent indicator of poor outcome.

According to Weir et al.[40] serum uric acid can be an independent predictor of poor outcome and future vascular events after acute stroke.

In his study serum uric acid concentrations was measured in an unselected cohort study of stroke survivors and was followed up. Uric acid was associated with a statistically significant three fold

increase in relative risk of death, even after adjustment for other conventional risk factors.

Uric acid being an anti oxidant, it is increased as a compensatory mechanism to protect the ischemic tissues of the brain from free radical injury[41]. Present observation concurs with the above statement.

Recent evidence suggests that acute ischemic stroke results in generation of local oxidants that augment local injury and increase infarct size. Acute stroke is associated with a rapid decrease in serum antioxidants that recover slowly over subsequent weeks[42]. Though uric acid is considered an antioxidant, it being an aqueous antioxidant, it can become a pro-oxidant under certain circumstances, particularly if other antioxidants such as ascorbate are low[43]. Thus fall in ascorbrate (Vitamin C) levels with acute stroke could predispose the serum uric acid to take on pro-oxidant properties. Acute stroke cases with high uric acid and low acerbate levels had worst outcome in a study carried by Cherubini et al[44].

However, it has been evident by experiments that uric acid is synthesised locally from infarcted tissues, particularly during reperfusion and its level in serum rises often in proportion to the size of the infarcted tissue, reperfusion status and the extent of the free radical injury.

So elevated uric acid though not, an abnormality and only a response to physiological stress, and to some extent is a biochemical marker of oxidative stress. As definite correlation between oxidative stress and serum uric acid level was not made earlier, therapeutic intervention for elevated uric acid should not be undertaken. However, it still can be used a surrogate biochemical marker for the oxidative stress in acute ischemic stroke. The elevated uric acid may indirectly reflect high amount of oxidative stress and therefore poor outcome in stroke patients.

To ascertain the above statement, large series of cases of stroke has to be studied along with other variables for oxidative stress and compared with uric acid.

SUMMARY

PURPOSE

To estimate the level of serum uric acid in patients with acute ischemic stroke, to find out its association with diabetes and hypertension, to correlate with age and gender and to study its significance in the out come of the stroke patients.

METHODS

A cross section study was designed after institutional ethical clearance to screen acute ischemic stroke patients admitted to the hospital within 48 hours of stroke who satisfied a rigid inclusion and exclusion criteria. Another 40 members with similar variables without stroke were taken as control. The serum uric acid level was measured by uricase method. The outcome in the stroke patients was analysed at the end of 2 weeks while in hospital. The data were entered in microsoft excel spread sheet and analysed statistically.

Results

There were 102 stroke patients. Among them there were 66 males and 36 females. Their age varied from 30 to 70 years and the mean age was 56.72 years. The uric acid level among the stroke cases varied from 4.12 to 7.2 mg/dL and the mean serum uric acid level was 5.66 mg/dL. It was elevated significantly than the control group ($P< 0.001$). Stroke patients with diabetics and hypertension

had elevated serum uric acid level than the counter parts in the control and the difference was significant statistically ($P<0.001$). Those stroke cases with elevated uric acid had poor outcome and statistically was significant ($P < 0.001$).

Conclusion

Serum uric acid level was increased in stroke patients and was independent of age and gender. Uric acid level among stroke cases was independent of their diabetic and hypertensive status. All the stroke cases who had poor outcome were found to have elevated uric acid level which may be a response to oxidative stress and hence it can be considered as biochemical marker in stroke patients.

CONCLUSION

1. Serum Uric Acid was higher in stroke patients than the control group and it was significant ($P < 0.001$).

2. Age and gender did not influence the serum uric acid level in the stroke patients.

3. Uric acid level was elevated in stroke cases with diabetics and hypertension and it was significant ($P<0.001$).

4. Among stroke cases, uric acid level was independent of diabetes and hypertension.

5. Stroke patients with elevated uric acid had poor outcome and it was significant ($P<0.001$).

6. Uric acid has been considered as a surrogate biochemical markers of oxidative stress in acute ischemic stroke. Elevated uric acid among stroke patients concurred with previous publication.